Can Fulvenes Form from Enediynes? A Systematic High-Level Computational Study on Parent and Benzannelated Enediyne and Enyne−Allene Cyclizations

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Apart from the well-known Bergman, Myers−Saito, and Schmittel ring closure reactions of parent enediyne (**4**) and enyne−allene (**3**), novel cyclization modes were identified using density functional (DFT) and coupled-cluster methods. The geometries obtained with several DFT functionals are quite similar; for consistency's sake, we employed BLYP/6-31G* geometries; Brueckner double energy single points [BCCD(T)/cc-pVDZ] on these geometries were used to determine the relative energies. The C^1-C^5 cyclization of **4** leading to fulvene biradical **8** is 40 kcal mol^{-1} endothermic, and the product lies 31 kcal mol^{-1} above 1,4-didehydrobenzene **7** because of the lack of aromatic stabilization. The heat of formation ($\Delta_f H°$) of **8** is predicted to be 172.0 ± 1.0 kcal mol^{-1}. Yet another ring closure of **4** leading to dimethylenecyclobutene biradical **12** is 69 kcal mol^{-1} endothermic and is hardly of preparative interest. A new cyclization of **3** should lead to the seven-membered ring biradical **13**, which is located 33 kcal mol^{-1} above **3** and 24 kcal mol^{-1} above the Schmittel product **6**. As the transition structure for both cyclizations differ by 11 kcal mol^{-1}, **13** may form under suitable conditions. All other possible modes of cyclization of **4** did not lead to stable products. Benzannelation has a significant effect on the endothermicities of the Bergman and Myers−Saito cyclizations, which are 8−9 kcal mol^{-1} above the parent reactions due to reduced aromatization energy in the naphthalene derivatives. The endothermicities of the other cyclization pathways are largely unaffected by benzannelation.

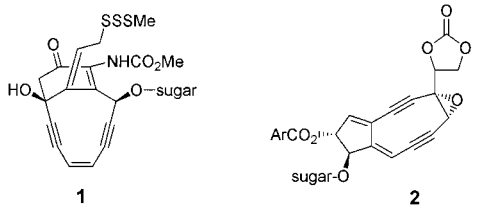
Introduction

The ring closure reactions of some polyunsaturated systems, such as enediynes or enyne−allenes, which are known as Bergman,[1−4] Myers−Saito,[5−9] and Schmittel cyclizations,[10−15] are of particular significance both for medicinal and organic materials chemistry.[16−22] Such or structurally related moieties lead to DNA-cleaving biradicals, i.e., they are potent antitumor drugs.[23−26] Naturally occurring examples are Calicheamicin γ^I_1 (**1**) or Neocarzinostatin (**2**) (Scheme 1).[16,17,20,22] The parent reactions are now well understood both experimentally[13,26−39] and theoretically.[40−53] Although many modes of cyclization can be envisaged, only three principally different ones are known experimentally. However, as we wish to demonstrate in this paper, other entirely unexplored cyclization modes of enediyne and enyne−allene substrates are possible. In particular, this study includes details on a new and important five-membered ring closure of the enediyne parent system giving rise to fulvene derivatives.

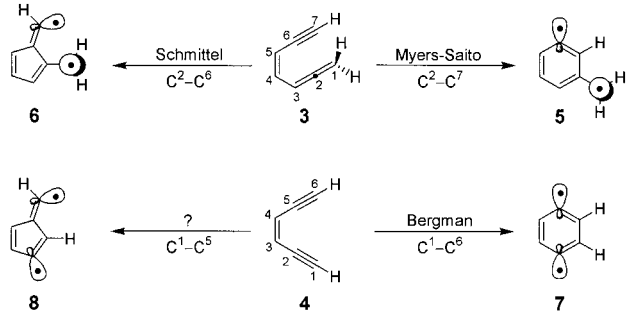
Background

The exothermic (−15 ± 3 kcal mol^{-1}) C^2-C^7 cycloaromatization of (*Z*)-1,2,4-heptatriene-6-yne (**3**, Myers−Saito cyclization) leads to α,3-didehydrotoluene (**5**, Scheme 2), a σ,π-biradical which is stabilized by benzylic π-conjugation;[5−8] a similarly aromatic biradical stems from the C^1-C^6 cyclization of (*Z*)-1,5-hexadiyne-3-ene (**4**, Bergman-cyclization).[1−4] In marked contrast to **5**, 1,4-didehydrobenzene (**7**) is a nonconjugated σ,σ-biradical (Scheme 2) which forms endothermically (8.5 ± 1.1 kcal mol^{-1}),[54] i.e., only at rather high temperatures (cyclization temperature ca. 200 °C). In the presence of a suitable H-donor such as 1,4-cyclohexadiene or even DNA, the subsequent formation of two new C−H bonds is highly exothermic and renders the overall reaction irreversible. For both

SCHEME 1: Antitumor Antibiotics Calicheamicin γ^I_1 1 and Neocarzinostatin 2



SCHEME 2: Cyclizations of Enyne−Allene 3 and Enediyne 4



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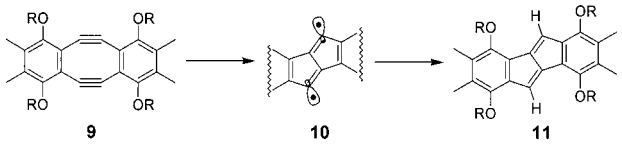
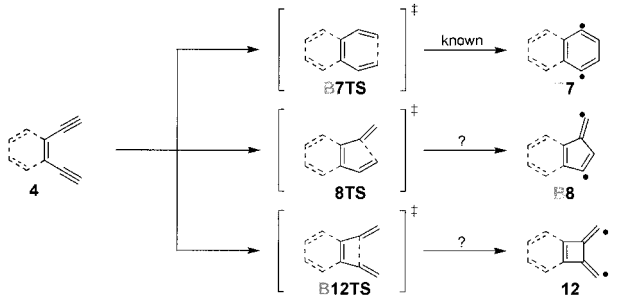
SCHEME 3: Synthesis of Indeno[2,1-a]indene Derivative 11 from Dibenzocyclyne 9 via the Suggested Biradical Intermediate 10



SCHEME 4: Cyclization Modes of the Parent Enediyne 4



reactions, the driving force is the gain of aromatization energy by forming a benzenoid system from an open-chain molecule. Hence, both biradicals are stabilized by about 21 kcal mol^{-1} due to the aromaticity; **5** gains another ~13 kcal mol^{-1} from benzylic π-conjugation.[55,56]

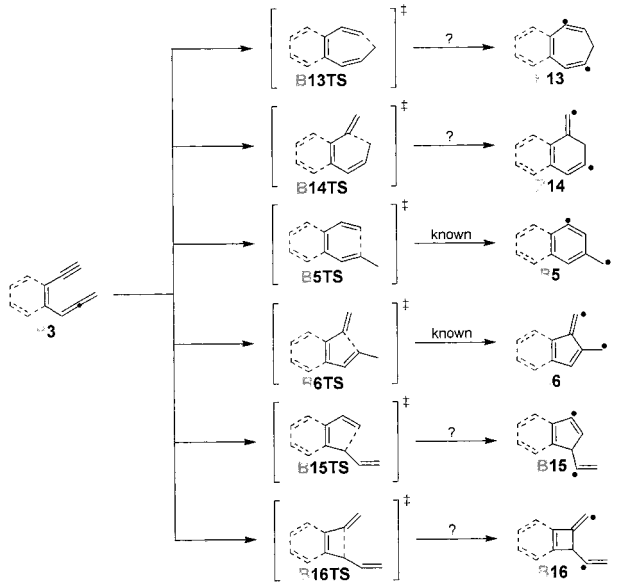
The C^2−C^6 cyclization of **3** (Schmittel cyclization), which gives rise to the methyl fulvene biradical (**6**), is obviously not driven by cycloaromatization (Scheme 2) and is therefore quite unfavorable.[10−13] Although **6** is a σ,π-biradical like the Myers−Saito product **5**, it lacks the aromatization energy which makes the Schmittel cyclization endothermic by about 10 kcal mol^{-1} (computed at MR-CI+Q/DZP[47] and BCCD(T)/cc-pVDZ[53]). However, the Schmittel reaction becomes energetically favorable when the acetylenic hydrogen in **3** is replaced by bulky groups like phenyl, *tert*-butyl, or trimethylsilyl.[10−15,26,36−39] These substituents raise the Myers−Saito cyclization barrier due to steric hindrance in **5** and, in the case of phenyl, lower the barrier for the Schmittel cyclization by radical stabilization through conjugation.

A comparison of the three known reactions makes a hitherto unknown C^1−C^5 cyclization of the enediyne **4** quite conceivable (Scheme 2), giving rise to the fulvene biradical (**8**). As the Schmittel reaction is energetically about 25 kcal mol^{-1} disfavored relative to the Myers−Saito reaction, it appears likely, however, that the C^1−C^5 ring closure of **4** is even more endothermic than the Bergman cyclization. An indication for the existence of the C^1−C^5 cyclization reaction comes from the observation that indeno[2,1-a]indene derivative **11** forms from dibenzocyclyne **9**, a cyclic system akin to **4**. It was suggested that the reaction proceeds via biradical intermediate **10**, which resembles a derivative of **8** (Scheme 3).[57]

If the C^1−C^5 reaction is a possibility, further cyclization modes of **3** and **4** (Schemes 4 and 5) must be considered. Enediyne **4** may also undergo a C^2−C^5 ring closure, giving rise to the dimethylenecyclobutene biradical **12**. All reactions depicted in Scheme 2 seem to take place only by interaction of sp-hybridized carbon centers. In **3**, however, there are additionally two sp^2 centers which may also be able to participate in a cyclization reaction. Hence, **3** may, at least in theory, undergo two ring closures between sp-hybridized and four between sp- and sp^2-hybridized carbon centers.

This report reveals new cyclization modes for the parent structures **3** and **4** (Schemes 4 and 5) which have, at least to

SCHEME 5: Cyclization Modes of the Parent Enyne−Allene 3



the best of our knowledge, not been described before. The barriers (**5TS**-**8TS**, **12TS**-**17TS**) and reaction energies leading to biradical products **5**−**8** and **12**−**16** are computed using density functional theory (DFT), which is able to describe the biradical products reasonably well. Improved energies are derived from coupled-cluster computations utilizing Brueckner orbitals [BCCD(T)]. The section "Computational Approach" details the choice of the theoretical level. All results are validated against known reactions whenever possible. Additionally, the effect of benzannelation on the cyclizations is also examined. Clear predictions regarding the experimental realization of the new reactions are made.

Computational Approach

The description of organic reactions including diradicaloid intermediates or transition structures remains a major challenge in quantum chemistry.[58−63] The difficulties arise from the fact that in biradical species with a small singlet−triplet separation (ΔE_{ST}) the approximate wave function can in some cases attain a lower electronic energy by breaking the spatial or spin symmetries present in the exact wave function.[64−67] Hence, single-reference techniques like the unrestricted (U) Hartree−Fock (HF) method,[68−70] or perturbation theory approaches (MP*n*),[71,72] in which a discrete electronic configuration is described by a single or perturbed reference wave function, respectively, cannot handle such problems. Methods which allow the proper mixings of competing, near-degenerate valence-bond structures are, generally, computationally extremely time-demanding. Standard approaches to spin or spatial symmetry-breaking problems are multireference techniques like the complete active space self-consistent field (CASSCF)[73−76] or the multireference configuration interaction (MR−CI) methods.[77−79] Another approach is represented by the Brueckner doubles (BD)[80−85] ansatz, a coupled-cluster[86−89] derivative in which the molecular orbitals are rotated in the presence of the correlation perturbation that the resulting single-excitation cluster amplitudes vanish. This procedure avoids problems which occur sometimes in the case of small singlet−triplet gaps for coupled-cluster theory with unmodified molecular orbitals.[50] These methods are highly successful because even the effects of nondynamical electron correlation are incorporated to a large

degree into the approximate wave function which avoids symmetry breaking.

An alternative to these highly accurate but extremely time-consuming methods is offered by nonlocal density functional theory (DFT)[90] because in comparison to HF theory, DFT is less prone to artifactual spatial and spin symmetry breaking.[67,91−94] Recent articles demonstrate impressively the usefulness of this approach for the description of diradicaloid species as thus occur in bond-breaking or ring-closure reactions.[95−104] It was emphasized that this technique can handle spin symmetry breaking problems efficiently and gives results of reasonably high accuracy without the time-demand of mutireference methods. Furthermore, the unrestricted broken-spin (BS-U) approach in which spatial and spin symmetries of the wave function are broken by mixing the frontier molecular orbitals allows the inclusion of some static electron correlation.[46,105,106] This approach allows for dealing with pure or nearly pure open-shell singlet states without the problems associated with partial orbital occupancies, and it avoids the collapse of the unrestricted SCF (self-consistent field) procedure to the restricted solution. Hence, earlier publications treating biradicals such as *para*-benzynes as pure closed-shell singlets[46,51,101] (i.e., using a restricted wave function) should be abandoned. This conclusion is well supported by the finding that the structure of **7** computed at the BS-UBLYP level of theory[53,107−109] is much closer to the CASSCF(8,8) than the RBLYP geometry (Figure 1). The importance using an unrestricted, broken-symmetry wave function was emphasized in a very recent insightful discussion.[103]

For completeness sake, we also compared the optimized structures of **3**−**8** at CASSCF(8,8)/6-31G* (using natural orbitals) and BLYP/6-31G* (Figure 1). In general, the structural differences are minor (with the exception of **6**, where the exocyclic CCH-angle deviates by about 28°). Single-point energy evaluations at BCCD(T)/cc-pVDZ were then performed on the optimized structures. As the BCCD(T) energies are consistently lower for the BLYP structures, this seems to indicate that these are probably a somewhat better description of the geometries if they were optimized at the coupled cluster level. Unfortunately, these types of routine optimizations are currently not yet feasible, but we are confident that the geometries chosen here are suitable for the higher level single points and for qualitative comparisons.

The vexing question whether DFT is applicable to multireference problems cannot be answered in general terms. The underlying problem is whether there is a single electronic configuration which produces a nearly complete density for an apparent multireference problem. This is a case-to-case decision and cannot be answered a priori. Hence, the applicability of DFT to such systems has to be tested individually. We will demonstrate that this approch indeed is valid for the biradical systems under consideration. Final energies were evaluated at a much higher level.

Since the products and TSs of the discussed reactions display varying degrees of biradical character, which is evident from the small singlet−triplet separations (ΔE_{ST}, Table 1),[64,65] HF-based single-reference methods are not suitable for the description of the cyclization reactions, and multireference post Hartree−Fock techniques are too time-consuming for large geometry optimizations. As discussed above, DFT offers a reasonable compromise for this quantum mechanically demanding problem.[46,50,51,101] To arrive at stable unrestricted solutions and to destroy spatial and α/β-symmetries, a BS-U ansatz was used for open-shell singlets. From a practical point of view, DFT methods utilizing BS-U wave functions offer a suitable compromise for diradical structure optimizations under consideration in the present paper.

TABLE 1: Singlet−Triplet Separations (ΔE_{ST}) of Selected Structures; Energies Were Obtained at the UBLYP/6-31G* Level of Theory (BS-U for Singlets)

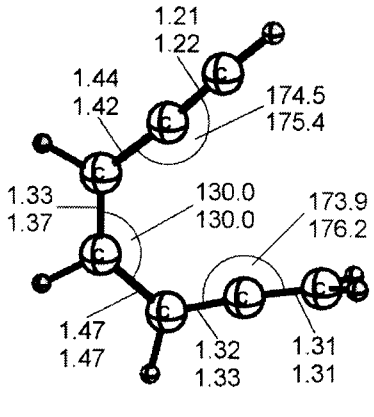
structure	ΔE_{ST} [kcal mol^{-1}][a]
7	−4.1[b]
8	−8.5
12	−1.2
5	−0.6
6	2.7
13	0.1
B7	−4.6
B8	−7.8
B12	−1.2
B5	−0.5
B6	0.3
B13	−0.1

[a] A negative value indicates a singlet ground state. [b] Experimental value: 3.8 ± 0.4 kcal mol^{-1}.[63]

There is still much discussion regarding the most suitable functional; this also includes whether a distinction between pure and hybrid functionals should be made. Although some systematic comparisons are available,[103] we extend these studies and compare here the results obtained at a large number of common DFT variants against experimental data, i.e., the barriers and reaction enthalpies of the Bergman and the Myers−Saito reactions. For proper comparison with the experiment, the reaction enthalpies were both evaluated at 298.15 K, and the barrier of the Bergman and Myers−Saito reactions were also determined at 470.15 and 343.15 K, respectively. In the case of the predicted cyclizations, we only discuss zero-point corrected reaction enthalpies and barriers at 0 K ($\Delta_0 H$, or $\Delta_0 H^{\ddagger}$, respectively), since mainly electronic effects influence the reaction mode. All HF, MP2, CCSD(T), BD(T), CASSCF, and the DFT computations including the B (Becke's 1988),[107] S (Slater's),[110−112] LYP (Lee, Yang, and Parr's),[108,109] PW91 (Perdew and Wang's 1991),[113] P86 (Perdews 1986),[114] PL (Perdew's local non-gradient corrected),[115] VWN (Vosko, Wilk and Nosair's),[116] VWN5,[116] or B3 (Becke's three parameter hybrid)[117] functionals were carried out with Gaussian94.[118] For newer DFT functionals {the combinations including the MPW (Baron's modified PW)[119] or the G96 (Gill's 1996)[120,121] functionals}, we employed Gaussian98.[122] The reaction enthalpies ($\Delta_{298}H$)[6,54] and barriers of the Bergman ($\Delta_{470}H^{\ddagger}$)[54] and the Myers−Saito ($\Delta_{343}H^{\ddagger}$)[5] cyclizations computed at various DFT levels and some post Hartree−Fock methods are summarized in Scheme 6.

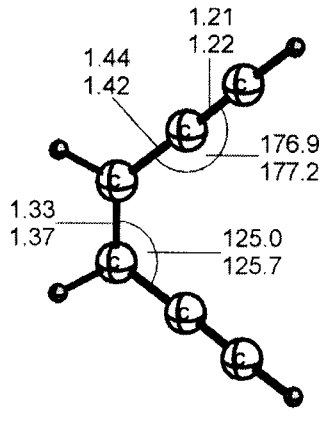
While the best results are obtained with combinations including the correlation functional of Lee, Yang, and Parr, the choice of the exchange functional has a smaller effect on the quality of the DFT results; only Slater's exchange functional performs poorly and seems to suffer from the lack of gradient corrections. Since it was shown earlier that the solutions for pure DFT functionals are somewhat less prone to symmetry-breaking,[105] MPWLYP, G96LYP, and BLYP are, arguably, good candidates for a compromise between chemical accuracy and computational demand; note, however, that B3LYP also was advovated recently.[123] Earlier treatises on the Bergman and related cyclizations used either the BPW91[50,101] or the BLYP[51−53] functionals. Since up to now the performance of the rather new G96LYP functional has not been tested against a larger set of reference molecules, we selected BLYP as our method of choice for consistency with earlier work.

The basis set dependence was also checked by systematically enlarging the basis from DZ- to TZ-type valence descriptions



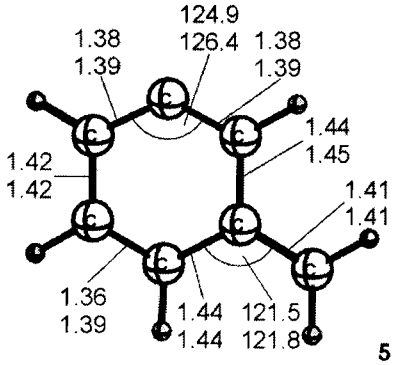
3

$E_{BD(T)//CASSCF(8,8)} = -269.42529$
$E_{BD(T)//BLYP} = -269.43012$ } $\Delta E = 3.0$ kcal mol^{-1}



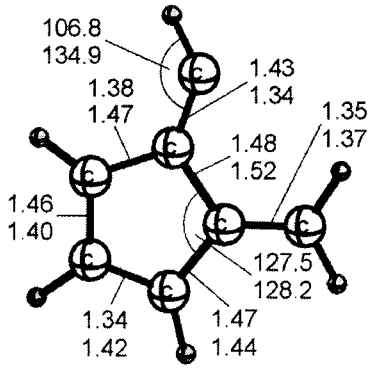
4

$E_{BD(T)//CASSCF(8,8)} = -230.22550$
$E_{BD(T)//BLYP} = -230.22929$ } $\Delta E = 2.4$ kcal mol^{-1}



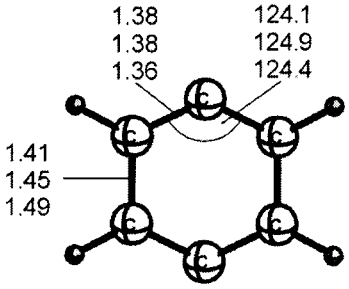
5

$E_{BD(T)//CASSCF(8,8)} = -269.45037$
$E_{BD(T)//BLYP} = -269.45448$ } $\Delta E = 2.6$ kcal mol^{-1}



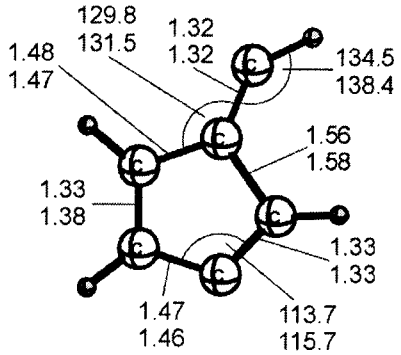
6

$E_{BD(T)//CASSCF(8,8)} = -269.40431$
$E_{BD(T)//BLYP} = -269.41606$ } $\Delta E = 7.4$ kcal mol^{-1}



7

$E_{BD(T)//CASSCF(8,8)} = -230.21759$
$E_{BD(T)//BLYP} = -230.21939$ } $\Delta E = 1.1$ kcal mol^{-1}



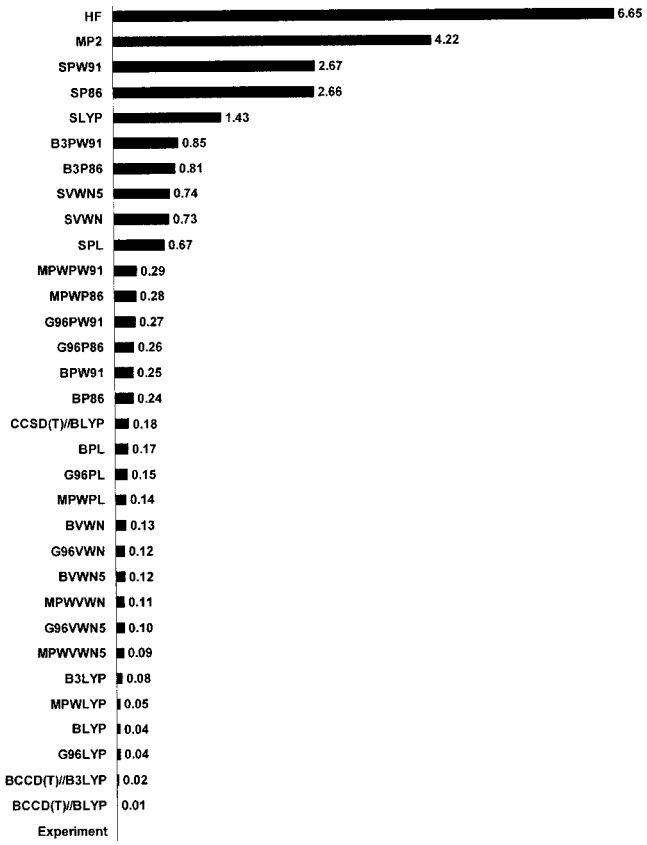
8

$E_{BD(T)//CASSCF(8,8)} = -230.16400$
$E_{BD(T)//BLYP} = -230.16676$ } $\Delta E = 1.7$ kcal mol^{-1}

Figure 1. Structural parameters of **3**−**8** at CASSCF(8,8)/6-31G* (first entry) and BLYP/6-31G* (second entry, UBS−BLYP for biradicals). For *para*-benzyne (**7**), the RBLYP/6-31G* geometry is also shown (last entry). For comparison, BCCD(T)/cc-pVDZ energies (unrestricted for biradicals) were evaluated for the CAS and BLYP structures; note that the BLYP structures give consistently lower BCCD(T) energies (positive ΔE).

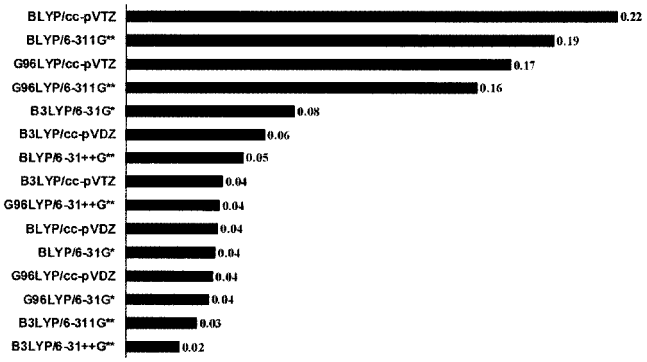
(Scheme 7). As often found for DFT, the behavior on increasing the basis set becomes erratic, in particular for pure functionals (BLYP and G96LYP were tested), where cc-pVTZ worsens the cc-pVDZ results (the same is found for 6-311G** vs 6-31G*). B3LYP behaves more consistently but does not necessarily give improved results with a better basis set (compare B3LYP/6-311G** vs B3LYP/6-31++G**). While this is overall somewhat discouraging, this may hold some clues regarding DFT in general. Within the scope of this paper, we were interested in identifying a suitable compromise between method and basis set size; BLYP/6-31G* and G96LYP/6-31G* both seem acceptable in this respect. Again, for consistency's sake and for comparison with earlier work, we chose BLYP/6-31G* for geometry optimizations. One referee prompted us to emphasize

SCHEME 6: Comparison of Computational and Experimental Data for the Bergman and Myers−Saito Reactions Utilizing Various DFT Functionals (BS-U for the Products, with the 6-31G* for DFT and the cc-pVDZ Basis Set for the Coupled-cluster Computations)[a]



[a] All enthalpies were evaluated at the respective experimental temperature. Every entry is composed of four computed and experimental values, determined from a total of 321 single computations. Presented is the average normalized error square of each method.

SCHEME 7: Comparison of the Computational and Experimental Data for the Bergman and Myers−Saito Reactions Obtained from the Best Three DFT Methods Employing Various Basis Sets[a]



[a] Presented is the average normalized error square of each method and basis set.

that the BS-UDFT approach may work well due to overall error cancellation and that this need not be true for other biradical systems. We therefore emphasize again that the use of DFT for these apparent multireference cases must both be treated individually and be accompanied by higher-level energy evaluations, as done in the present paper. As all geometries at the "acceptable" DFT levels of theory are very similar, our final energy evaluations at BCCD(T)/cc-pVDZ are nearly unaffected by the choice of optimization level.

TABLE 2: Comparison of Computed and Experimental $\Delta H^{\ddagger}$ and ΔH_{298} Values of the Bergman and Myers−Saito Reactions (in kcal mol^{-1})

		BLYP/6-31G*	BCCD(T)/cc-pVDZ[a]	experiment
	**7TS**	23.8	25.6	28.2 ± 0.5[53]
	**7**	7.3	7.0	8.5 ± 1.1[53]
	**B7TS**	23.0	27.6	25.2 ± 0.8[125]
	**B7**	13.2	16.4	17.8 ± 1.2[125]
	**5TS**	17.8	19.7	21.8 ± 0.8[5]
	**5**	−10.8	−14.8	-15 ± 3[6]

[a] Geometries and thermal corrections from BLYP/6-31G*.

As demonstrated in Scheme 6, the quality of our results is further improved by single-point computations on the BLYP/6-31G* structures utilizing the Brueckner-doubles coupled-cluster approach, including triple excitations perturbatively {BCCD(T), also called BD(T)} on the basis of BS-UHF reference wave functions. In contrast, coupled-cluster computations with unmodified UHF molecular orbitals {CCSD(T)} gave poor results. This may be due to the fact that in some open-shell cases, CCSD(T) overestimates the single-cluster amplitudes. The use of Brueckner orbitals, in which the singles contribution is zero due to orbital rotation, leads to a significant improvement.[124]

The approach employed in the present paper combines BLYP/6-31G*[125] structures, thermal, and ZPVE corrections for the BCCD(T) relative energies. The BCCD(T) single-point computations utilized Dunning's correlation-consistent double-ζ basis set with one set of polarization functions on all atoms (cc-pVDZ). To validate and to emphasize the predictive quality of our theoretical approach, all experimentally known energies for the Bergman and Myers−Saito reactions were compared to data computed at the described level (Table 2).

The data of Table 2 and Scheme 6 show that the computationally inexpensive BLYP/6-31G* level reproduces the experimental data reasonably well, while the BCCD(T)/cc-pVDZ results are roughly within the experimental errors. With this convincing agreement of experimental and computed data at hand, further predictions regarding the cyclizations in question can now be made (Table 3). Unless noted otherwise, we discuss energies obtained at BCCD(T)/cc-pVDZ//BLYP/6-31G* + ZPVE.

Results and Discussion

Enediyne Cyclizations. As the transition structure for the Schmittel cyclization **6TS** is about 7 kcal mol^{-1} above **5TS** (Myers−Saito reaction) and the Schmittel product **6** is about 24 kcal mol^{-1} less stable than the Myers−Saito product **5**, it is quite understandable that **6** has not yet been detected as a possible product of the cyclizations of the *parent* enyne−allene system. This situation changes when the acetylenic hydrogen is replaced by bulky groups (vide supra). As we have shown recently, the Schmittel reaction can also be favored over the Myers−Saito mode by incorporating enyne−allenes into strained

TABLE 3: Barriers and Reaction Enthalpies (Δ_0H) of the Enediyne (4) and Enyne−Allene (3) Cyclizations (in kcal mol^{-1})

type of reaction	structure	BLYP/6-31G*	BCCD(T)/cc-pVDZ[a]
enediynes	**4**	0.0	0.0
	7TS	25.2	27.1
	7	8.5	8.3
	8TS	41.0	42.1
	8	41.3	39.6
	12TS	–	–
	12	68.8	69.0
benzannelated enediynes	**B4**	0.0	0.0
	B7TS	24.6	29.2
	B7	14.4	17.6
	B8TS	37.2	41.6
	B8	37.4	38.7
	B12TS	67.3	71.8
	B12	67.9	70.9
enyne−allenes	**3**	0.0	0.0
	5TS	18.7	20.6
	5	−9.7	−13.7
	6TS	25.4	27.9
	6	12.9	8.8
	13TS	36.5	37.8
	13	34.9	32.9
benzannelated enyne−allene	**B3**	0.0	0.0
	B5TS	19.5	23.1
	B5	−4.5	−5.8
	B6TS	25.2	28.4
	B6	11.9	9.4
	B13TS	36.7	40.7
	B13	35.5	33.3

[a] Geometries and thermal corrections from BLYP/6-31G*.

Figure 2. Delocalized vs localized spin densities of the Schmittel product **6** and the fulvene biradical **8**.

cyclic systems.[53a,129] In a previous computational study, we found that an eight-membered ring enyne−allene favors the Schmittel product because of a lower barrier and slightly less unfavorable endothermicity compared to the corresponding Myers−Saito reaction. The nine-membered enyne−allene also gives the Schmittel product under kinetic control; other ring sizes favor the Myers−Saito cyclization.

The yet unknown C^1-C^5 cyclization of the parent enediyne system **4** giving rise to the fulvene biradical **8** is more endothermic than the analogous Schmittel reaction. Structure **8** is also much higher in energy than **7**, as it lacks both aromatization and benzylic π-conjugation (Figure 2). As a consequence, the fulvene-path transition structure **8TS** (42.1 kcal mol^{-1}) is located 15 kcal mol^{-1} above that of the Bergman cyclization (**7TS**); **8** (39.6 kcal mol^{-1}) is 31 kcal mol^{-1} less stable than **7**. Hence, in agreement with all experimental observations, **8** is not likely to form from the cyclization of **4**. For further study, it is nevertheless instructive to analyze the electronic structure of **8**. This aids in answering the question under what circumstances this cyclization may be realized.

There are two isomers of the fulvene biradical which differ in the configuration of the hydrogen at the exocyclic double bond (Figure 2). The (*Z*)-configuration **8a** is 2.7 kcal mol^{-1} more stable than the (*E*)-isomer **8b** because there is a stabilizing interaction of the sp^2 orbital at C^6 and the antibonding orbital of the C^1-C^5 bond (numbering see Scheme 2). The analogous interaction with the C^4-C^5 antibonding orbital in **8b** is smaller, which is also evident from the differences in bond lengths (C^1-C,[5] **8a** 1.582 Å and **8b** 1.537 Å; C^4-C,[5] **8a** 1.474 Å and **8b** 1.488 Å) of the acceptor bonds. However, **8b** may play an important role in the cyclization of disubstituted enediynes when bulky groups try to minimize steric repulsion.

In marked contrast to the TS of the Bergman cyclization, the transition structure for the C^1-C^5 ring closure is highly biradicaloid. Optimizations along this cyclization path show that a proper TS indeed can only be located if a broken-spin open-shell (BS-UBLYP) wave function is used. Not unexpectedly, a closed-shell (RBLYP) approach yields a steady increase in energy with decreasing C^1-C^5 distance without going through a maximum (Figure 3). At the transition state, there is an energy gap between the unrestricted and the restricted approach (grey box, Figure 3). In contrast, the transition structure for the C^1-C^6 (Bergman) cyclization shows no biradical character, as noted in many computational studies before; i.e., there is no energy gap at the maximum of the energy profile between the closed-shell and the broken-spin open-shell ansatz.

The enthalpy of formation Δ_fH of **8a** can be predicted using an isodesmic equation (Table 4). This approach has been used recently to predict the Δ_fH of the Schmittel product **6** in a highly accurate way.[53] Comparison of the experimental (138.0 ± 1.0 kcal mol^{-1}) and computed (137.5 ± 2.0 kcal mol^{-1}) enthalpy of formation of **7** at the BCCD(T)/cc-pVDZ level of theory shows the predictive quality of our approach. Our best prediction for the $\Delta_fH°$ of **8a** is 172.0 ± 1.0 kcal mol^{-1}.

Another cyclization mode of **4**, also unknown thus far, is the formation of the dimethylenecyclobutene biradical **12** (Scheme

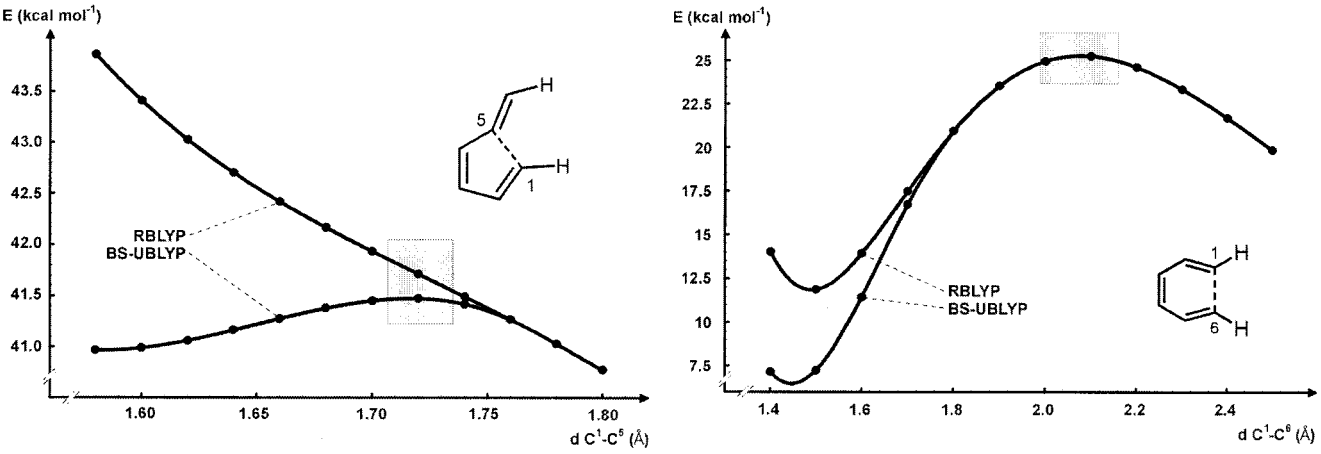


Figure 3. Closed- and open-shell C^1-C^5 (fulvene) and C^1-C^6 (Bergman) cyclizations of **4** at BLYP/6-31G*.

TABLE 4: Isodesmic Equation for the Determination of the Heat of Formation $\Delta_f H$ of 8a ($\Delta_f H$ Benzene = 19.81 kcal mol^{-1},[126] Fulvene = 53.6 kcal mol^{-1},[126] Dehydrobenzene = 138.0 ± 1.0 kcal mol^{-1})[53]

	$\Delta_R H$	$\Delta_f H$
BLYP/6-31G*	0.02	171.8 ± 1.0
BCCD(T)/cc-pVDZ	0.23	172.0 ± 1.0

[a] ZPVE taken from BLYP/6-31G* frequency computations.

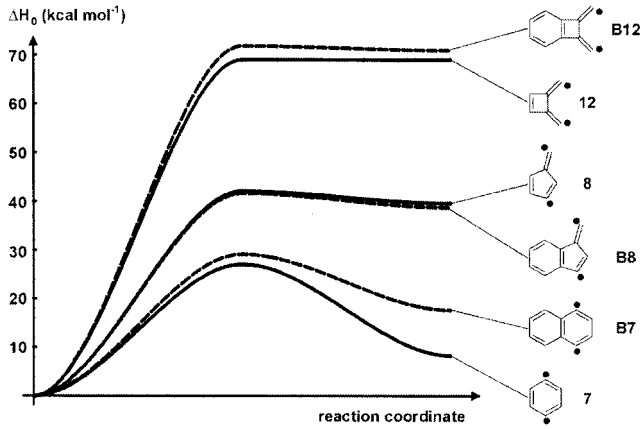


Figure 4. Comparison of the cyclization potential energy surfaces of the enediyne parent system **4** and its benzannelated derivative **B4** at BCCD(T)/cc-pVDZ//BLYP/6-31G*.

4). Not unexpectedly, this ring closure is even more endothermic than the C^1-C^5 cyclization (about 54 kcal mol^{-1} above **7**). Additionally, the corresponding transition structure **12TS**, which, despite extensive efforts, could not be determined exactly, is at most 5×10^{-3} kcal mol^{-1} above biradical **12**, so that this reaction would not be experimentally feasible.

Effect of Benzannelation. The benzannelated enediyne (1,2-diethynylbenzene, **B4**) undergoes the same reactions as **4**, but the energetics are somewhat different. As also observed experimentally (the rate-determining step is altered),[31] the Bergman cyclization giving rise to 1,3-didehydronaphthalene **B7** is more unfavorable than the parent reaction.[126] This is due to the fact that the total aromatization energy of naphthalene is smaller than that of two benzene rings.[127] The parent Bergman ring closure gains the full aromatization energy, while 1,3-didehydronaphthalene **B7** does not benefit from additional benzenoid stabilization through cycloaromatization of **B4**. This is exemplified by the exothermicity (−9.4 kcal mol^{-1}) of isodesmic equation 1.

As a consequence, transition state **B7TS** (29.2 kcal mol^{-1}) lies 2.1 kcal mol^{-1} above **7TS**, and **B7** is 9.4 kcal mol^{-1} less stable than **7** (Figure 4). As found for **7TS**, the **B7TS** has no biradical character. Partial loss of aromaticity in **B12** makes this reaction 2.0 kcal mol^{-1} more unfavorable than cyclization to **12**. In contrast to the parent system, the transition structure **B12TS** (71.8 kcal mol^{-1}) could be identified, but it is merely 0.9 kcal mol^{-1} above **B12** (Figure 4).

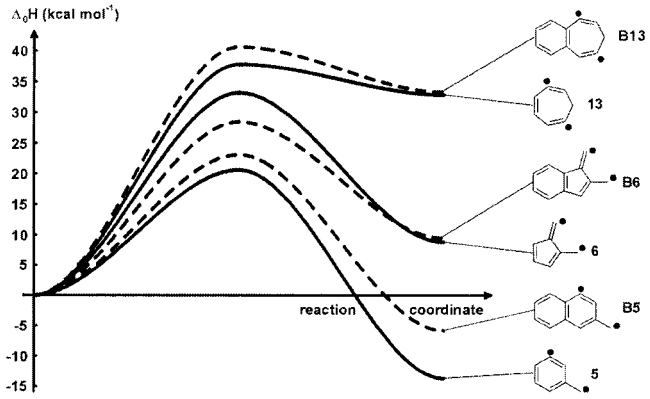


Figure 5. Comparison of the cyclization potential energy surfaces of the enyne−allene parent system **3** and its benzannelated derivative **B3** at BCCD(T)/cc-pVDZ//BLYP/6-31G*.

The benzannelated derivative of the fulvene biradical (1-methylene-1*H*-indene biradical, **B8**) is marginally stabilized relative to the parent system (0.9 kcal mol^{-1}); the same applies to **B8TS** (0.5 kcal mol^{-1}). As a consequence, cyclization does not take place in either reaction; i.e., there is no aromatic stabilization (Figure 4). Again, this is also evident from the almost thermoneutral (1.3 kcal mol^{-1}) isodesmic reaction described in equation 2. The transition structure is, like **8TS**, highly biradicaloid.

Enyne−Allene Cyclizations. As there is one more carbon atom which may be involved in the cyclization reactions, there are more hypothetical ring closures possible for enyne−allene **3** compared to **4**. In contrast to all $C_{sp}-C_{sp}$ reactions of the enediyne, sp^2-hybridized carbon atoms can now also partake in the ring closures.

The cyclization producing the seven-membered ring biradical (cycloheptatriene biradical **13**) by joining the terminal carbon atoms of **3** is the most promising with regard to its experimental verification. In contrast to the reactions known to date, the biradical is formed by the interaction of an sp and an sp^2 carbon, leading to a σ,σ-biradical. This cyclization is 31.7 kcal mol^{-1} endothermic, and **13** is about 23 kcal mol^{-1} less stable than the Schmittel product **6**. Since **6** is not observed in the cyclization of **3**, the formation of **13** is even less likely. However, the transition structure **13TS** (37.4 kcal mol^{-1}) is about 10 kcal mol^{-1} higher in energy than **6TS** for the Schmittel cyclization. Provided that suitable substituents can be found, the synthesis of derivatives of the seven-membered ring biradical **13** may nevertheless be viable. The transition state **13TS** has nearly no biradical character like that of the Myers−Saito and Schmittel reactions.

The benzannelated enyne−allene (1-ethinyl-2-propa-1,2-dienyl-benzene, **B3**) undergoes similar reactions as **3** and has an energy pattern similar to that of **4** and **B4** results. The benzannelated Myers−Saito product **B5** (−5.8 kcal mol^{-1}) is about 8 kcal mol^{-1} above **5** because of the reduced aromaticity in the naphthalene-like product (Figure 5). As the benzannelated Schmittel product **B6** does not form via a cycloaromatization reaction, the energy (9.4 kcal mol^{-1}) remains merely the same, and **B6** is only marginally destabilized by the benzene ring (∼0.7 kcal mol^{-1}).[128] The barrier and reaction enthalpy to formation of the 7H-benzocycloheptene biradical **B13** is virtually un-

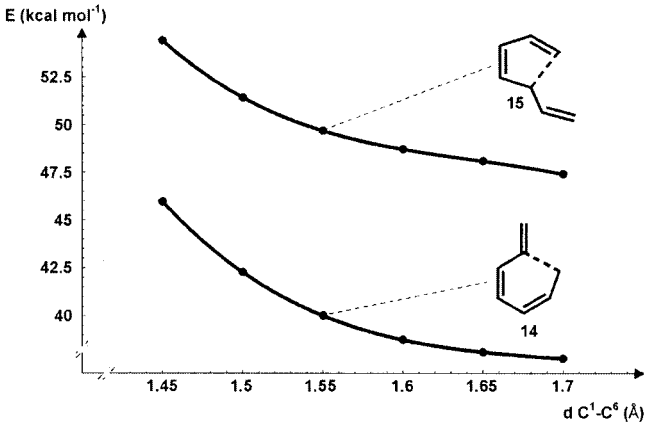


Figure 6. Energy surface of the C^3-C^7 and C^1-C^6 cyclizations at BLYP/6-31G*.

changed relative to the parent reaction. In contrast to all other enyne−allene ring closures, **B13TS** is biradicaloid.

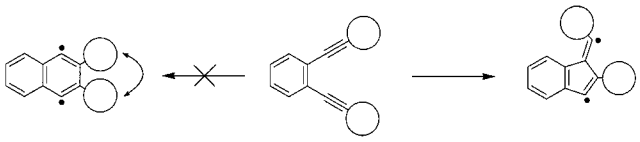
Other cyclization modes for **3** do not lead to stationary open-shell singlet biradical structures. Careful investigation of the C^3-C^7 and C^1-C^6 cyclization reaction coordinates showed a monotonic increase of the energies with decreasing C−C distances (Figure 6); the C^3-C^6 mode is similarly inaccessible. Therefore, these cyclizations can be excluded.

Concluding Remarks and Outlook

The present work demonstrates that there are, apart from the already well-known Bergman, Myers−Saito, and Schmittel reactions, other important cyclizations possible for enediynes and enyne−allenes. Some of these may be realized experimentally and are important for the synthesis of new hydrocarbon materials or potential antitumor antibiotics.

In elucidating the new reaction pathways, we first examined in detail the applicability of the most common DFT methods for the systems under consideration. This also aims at identifying reliable DFT approaches for systematically studying open-shell hydrocarbons which may otherwise only be treated with highly sophisticated multireference methods. The G96LYP, BLYP, and MPWLYP flavors are most suitable in conjunction with a 6-31G* basis set. Although the average errors with the highly popular B3LYP functional combination are only slightly larger, the danger of symmetry breaking disfavors this approach somewhat. The relative energies can be further improved utilizing BCCD(T)/cc-pVDZ single points on the BLYP/6-31G* geometries. Remarkably, the agreement between experiment and theory is on average within ± 1.5 kcal mol^{-1} at this high level of theory.

SCHEME 8: Schematic representation of a possible way of synthesizing fulvene derivatives from disubstituted enediynes



In addition to the C^1-C^6 (Bergman) ring closure, we found that enediyne **4** also undergoes a novel C^1-C^5 cyclization, giving rise to fulvene biradical **8**. Because of the lack of aromatic or conjugative stabilization of the radical sites, the reaction enthalpy is rather high (39.6 kcal mol^{-1}). The corresponding transition structure **8TS** is associated with a barrier of 42.1 kcal mol^{-1} and has, in contrast to that of the Bergman reaction (**7TS**), significant biradical character because of its late location along the reaction path. There are two isomers of product **8** which differ in the position of the hydrogen at the exocyclic double bond. Although the (*Z*)-isomer (**8a**) is 2.7 kcal mol^{-1} more stable than the (*E*)-isomer (**8b**), the latter may play an important role in the cyclization of disubstituted enediynes. With regard to the experimental verification of the predicted five-ring cyclization, we suggest that bulky groups at the enediyne termini should favor this mode over Bergman cyclization (Scheme 8), due to minimization of steric repulsion in the fulvene derivative. The problem, however, may be that this will increase the barriers for cyclization even more.

As the computed enthalpy of formation for *p*-benzyne **7** (determined by an isodesmic equation) agrees very well with experiment (137.5 ± 2.0 kcal mol^{-1} vs 138.0 ± 1.0 kcal mol^{-1}, respectively), a similar isodesmic approach confidently predicts $\Delta_f H°$ of **8a** to be 172.0 ± 1.0 kcal mol^{-1}.

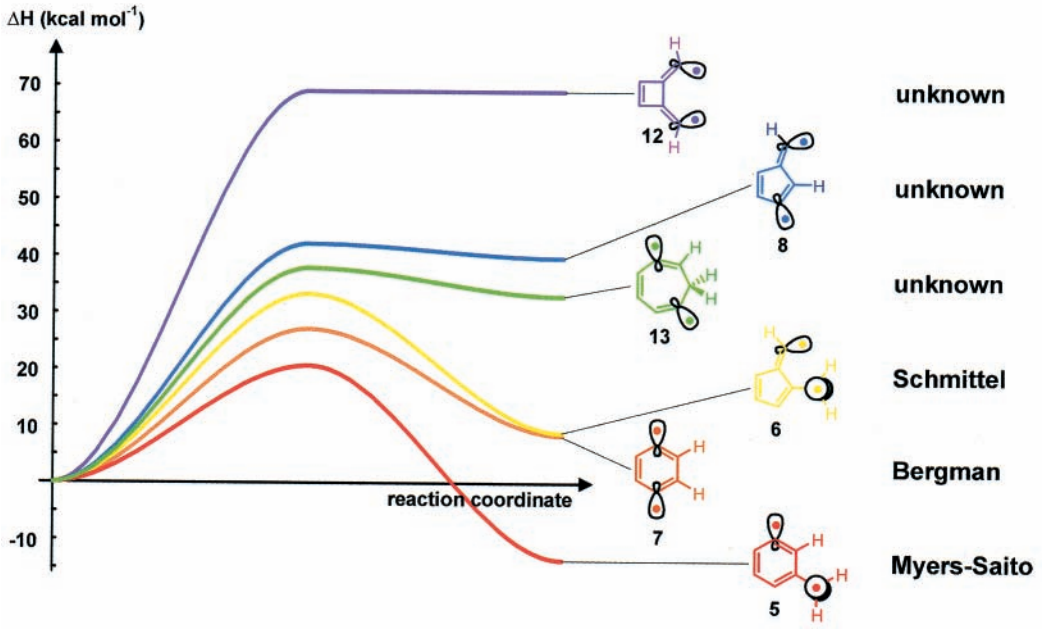


Figure 7. Comparison of the barriers and reaction enthalpies of the enediyne (**4**) and enyne−allene (**3**) parent system cyclizations.

For the enyne−allene **3**, a new C^1-C^7 cyclization giving rise to cycloheptatriene biradical **13** was also identified. This reaction is 31.7 kcal mol^{-1} endothermic and gives, in contrast to **5** and **6**, the σ,σ-biradical **13**. The reaction barrier, however, is 10 kcal mol^{-1} higher than that of the Schmittel path. All other theoretically possible cyclizations of **3** (C^1-C,[6] C^3-C,[7] and C^3-C^6) did not lead to stable open-shell singlet biradicals and can therefore be excluded.

In agreement with experimental observations, benzannelation has a large effect on the Bergman and Myers−Saito reaction. As one aromatic ring is already present in the benzannelated starting materials, the total aromatic stabilization energy is reduced in the products; both reactions are 8−9 kcal mol^{-1} more endothermic than the parent cyclizations. On the contrary, as the fulvene or seven-membered ring products only pertain the aromatic ring already present in the precursors, the effect of the benzanellation on the reaction enthalpies is negligible. However, while the fulvene cyclization barrier of the benzannelated enediyne is also largely unaffected, the respective barrier to Schmittel cyclization is reduced by about 5 kcal mol^{-1}.

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Supporting Information Available: Tables of energies and structures. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Jones, R. R.; Bergman, R. G. *J. Am. Chem. Soc.* **1972**, *94*, 660−661.
(2) Bergman, R. G. *Acc. Chem. Res.* **1973**, *6*, 25−31.
(3) Darby, N.; Kim, C. U.; Salaün, J. A.; Shelton, K. W.; Takada, S.; Masamune, S. *Chem. Commun.* **1971**, 1516−1517.
(4) Wong, H. N. C.; Sondheimer, F. *Tetrahedron Lett.* **1980**, *21*, 217−220.
(5) Myers, A. G.; Kuo, E. Y.; Finney, N. S. *J. Am. Chem. Soc.* **1989**, *111*, 8057−8059.
(6) Myers, A. G.; Dragovich, P. S.; Kuo, E. Y. *J. Am. Chem. Soc.* **1992**, *114*, 9369−9386.
(7) Nagata, R.; Yamanaka, H.; Okazaki, E.; Saito, I. *Tetrahedron Lett.* **1989**, *30* (37), 4995−4998.
(8) Nagata, R.; Hidenori, Y.; Murahashi, E.; Saito, I. *Tetrahedron Lett.* **1990**, *31*, 2907−2910.
(9) Myers, A. G.; Dragovich, P. S. *J. Am. Chem. Soc.* **1989**, *111*, 9130−9132.
(10) Schmittel, M.; Strittmatter, M.; Kiau, S. *Tetrahedron Lett.* **1995**, *36* (28), 4975−4978.
(11) Schmittel, M.; Kiau, S.; Siebert, T.; Strittmatter, M. *Tetrahedron Lett.* **1996**, *37(43)* , 7691−7694.
(12) Schmittel, M.; Strittmatter, M.; Kiau, S. *Angew. Chem.* **1996**, *108* (16), 1952−1954.
(13) Schmittel, M.; Keller, M.; Kiau, S.; Strittmatter, M. *Chem. Eur. J.* **1997**, *3* (5), 807−816.
(14) Gillmann, T.; Hülsen, T.; Massa, W.; Wocadlo, S. *Synlett* **1995**, 1257−1259.
(15) Garcia, J. G.; Ramos, B.; Pratt, L. M.; Rodriguez, A. *Tetrahedron Lett.* **1995**, *36(41)* , 7391−7394.
(16) Maier, M. E. *Synlett* **1995**, 13−26.
(17) Nicolaou, K. C.; Dai, W.-M. *Angew. Chem.* **1991**, *103*, 1453−1481.
(18) Nicolaou, K. C.; Smith, A. L.; Wendeborn, S. V.; Hwang, C.-K. *J. Am. Chem. Soc.* **1991**, *113*, 3106−3114.
(19) Nicolaou, K. *Chem. Ber.* **1994**, 33−36.
(20) Smith, A. L.; Nicolaou, K. C. *J. Med. Chem.* **1996**, *39*, 2103-2117.
(21) Brückner, R.; Suffert, J.; Abraham, E.; Raeppel, S. *Liebigs Ann.* **1996**, 447−456.
(22) Grissom, J. W.; Gunawardena, G. U.; Klingberg, D.; Huang, D. *Tetrahedron* **1996**, *52* (19), 6453−6518.
(23) Semmelhack, M. F.; Gu, Y.; Ho, D. M. *Tetrahedron Lett.* **1997**, *38*, 5583−5586.
(24) Myers, A. G.; Dragovich, P. S. *J. Am. Chem. Soc.* **1992**, *114*, 5859−5860.
(25) Nicolaou, K. C.; Maligres, P.; Shin, J.; de Leon, E.; Rideout, D. *J. Am. Chem. Soc.* **1990**, *112*, 7825−7826.
(26) Schmittel, M.; Maywald, M.; Strittmatter, M. *Synlett* **1997**, 165−166.
(27) Marquardt, R.; Balster, A.; Sander, W.; Kraka, E.; Cremer, D.; Radziszewski, J. G. *Angew. Chem.* **1998**, *110*, 1001−1005.
(28) Sander, W. *Acc. Chem. Res.* **1999**, *32*, 669−676.
(29) König, B. *Eur. J. Org. Chem.* **2000**, 381−385.
(30) König, B.; Pitsch, W. *J. Org. Chem.* **1996**, *61*, 4258−4261.
(31) Kaneko, T.; Takahashi, M.; Hirama, M. *Tetrahedron Lett.* **1999**, *40*, 2015−2018.
(32) Wang, K. K.; Zhang, H.-R.; Petersen, J. L. *J. Org. Chem.* **1999**, *64*, 1650−1656.
(33) Cunico, R. F.; Nair, S. K. *Tetrahedron Lett.* **1997**, *38* (1), 25−28.
(34) Wang, K. K.; Wang, Z.; Sattsangi, P. D. *J. Org. Chem.* **1996**, *61*, 1516−1518.
(35) Dopico, P. G.; Finn, M. G. *Tetrahedron* **1999**, *55*, 29−62.
(36) Schmittel, M.; Strittmatter, M. *Tetrahedron* **1998**, *54*, 13751−13760.
(37) Schmittel, M.; Steffen, J.-P.; Wencesla Angel, M. A.; Engels, B.; Lennartz, C.; Hanrath, M. *Angew. Chem.* **1998**, *110*, 1633−1635.
(38) Schmittel, M.; Steffen, J.-P.; Engels, B.; Lennartz, C.; Hanrath, M. *Angew. Chem.* **1998**, *110*, 2531−2533.
(39) Schmittel, M.; Steffen, J.-P.; Auer, D.; Maywald, M. *Tetrahedron Lett.* **1997**, *38(35)* , 6177−6180.
(40) Koga, N.; Morokuma, K. *J. Am. Chem. Soc.* **1991**, *113*, 1907−1911.
(41) Lindh, R.; Persson, B. J. *J. Am. Chem. Soc.* **1994**, *116*, 4963−4969.
(42) Lindh, R.; Lee, T. J.; Bernhardsson, A.; Persson, B. J.; Karlström, G. *J. Am. Chem. Soc.* **1995**, *117*, 7186−7194.
(43) Lindh, R.; Schütz, M. *Chem. Phys. Lett.* **1996**, *258*, 409−415.
(44) Lindh, R.; Ryde, U.; Schütz, M. *Theor. Chem. Acc.* **1997**, *97*, 203-210.
(45) Kraka, E.; Cremer, D. *Chem. Phys. Lett.* **1993**, *216*, 333−340.
(46) Kraka, E.; Cremer, D. *J. Am. Chem. Soc.* **1994**, *116*, 4929−4936. Note that we were unable to reproduce the reported ZPVE for *para*-didehydrobenzene at the MP2 level, where this species seems to be a transition structure (NIMAG=1) with a large, unreasonable imiginary frequency. This problem was recently clarified: Crawford, T. D.; Kraka, E.; Stanton, J. F.; Cremer, D. *J. Chem. Phys.* **2001**, *114*, 10638−10650.
(47) Engels, B.; Hanrath, M. *J. Am. Chem. Soc.* **1998**, *120*, 6356−6361.
(48) Engels, B.; Lennartz, C.; Hanrath, M.; Schmittel, M.; Marc, S. *Angew. Chem.* **1998**, *110*, 2067−2070.
(49) Cramer, C. J.; Nash, J. J.; Squires, R. R. *Chem. Phys. Lett.* **1997**, *277*, 311−320.
(50) Cramer, C. J. *J. Am. Chem. Soc.* **1998**, *120*, 6261−6269.
(51) Schreiner, P. R. *J. Am. Chem. Soc.* **1998**, *120*, 4184−4190.
(52) Schreiner, P. R. *Chem. Commun.* **1998**, *4*, 483−484.
(53) (a) Schreiner, P. R.; Prall, M. *J. Am. Chem. Soc.* **1999**, *121*, 8615−8627. (b) Cramer, C. J.; Kormos, B. L.; Seierstad, M.; Sherer, E. C.; Winget, P. *Org. Lett.* **2001**, *3*, 1881−1884.
(54) Roth, W. R.; Hopf, H.; Horn, C. *Chem. Ber.* **1994**, *127*, 1765−1779.
(55) Roth, W. R.; Ruf, G.; Ford, P. W. *Chem. Ber.* **1974**, *107*, 48−52.
(56) Schleyer, P. v. R.; Jiao, H. *Pure Appl. Chem.* **1996**, *68*, 209−218.
(57) Chakraborty, M.; Tessier, C. A.; Youngs, W. J. *J. Org. Chem.* **1999**, *64*, 2947−2949.
(58) Allen, W. D.; Horner, D. A.; DeKock, R. L.; Remmington, R. B.; Schaefer, H. F., III. *Chem. Phys.* **1989**, *133*, 11−45.
(59) Burton, N. A.; Yamaguchi, Y.; Alberts, I. L.; Schaefer, H. F., III *J. Chem. Phys.* **1991**, *95*, 7466−7478.
(60) Barnes, L. A.; Lindh, R. *Chem. Phys. Lett.* **1994**, *223*, 207−214.
(61) Crawford, T. D.; Stanton, J. F.; Allen, W. D.; Schaefer, H. F., III *J. Chem. Phys.* **1997**, *107*, 10626−10632.
(62) Sherrill, C. D.; Krylov, A. I.; Byrd, E. F. C.; Head-Gordon, M. *J. Chem. Phys.* **1998**, *109*, 4171−4181.
(63) Dehareng, D.; Dive, G. *J. Comput. Chem.* **2000**, *21*, 483−504.
(64) Wenthold, P. G.; Squires, R. R.; Lineberger, W. C. *J. Am. Chem. Soc.* **1998**, *120*, 5279−5290.
(65) Wenthold, P. G.; Wierschke, S. G.; Nash, J. J.; Squires, R. R. *J. Am. Chem. Soc.* **1994**, *116*, 7378−7392.

(66) Sherrill, C. D.; Lee, M. S.; Head-Gordon, M. *Chem. Phys. Lett.* **1999**, *301*, 425−430.
(67) Perdew, J. P.; Savin, A.; Burke, K. *Phys. Rev. A* **1995**, *51*, 4531−4540.
(68) Roothaan, C. C. J. *Rev. Mod. Phys.* **1951**, *23*, 69−89.
(69) Pople, J. A.; Nesbet, R. K. *J. Chem. Phys.* **1954**, *23*, 571−574.
(70) McWeeny, R.; Dierksen, G. *J. Chem. Phys.* **1968**, *49*, 4852−4856.
(71) Møller, C.; Plesset, M. S. *Phys. Rev.* **1934**, *98*, 5648−5652.
(72) Krishnan, R.; Pople, J. A. *Int. J. Quantum Chem.* **1978**, *14*, 91−100.
(73) Hegarty, D.; Robb, M. A. *Mol. Phys.* **1979**, *38*, 1795−1812.
(74) Eade, R. H. E.; Robb, M. A. *Chem. Phys. Lett.* **1981**, *83*, 362−368.
(75) Squires, R. R.; Cramer, C.; J. *J. Phys. Chem. A* **1998**, *102*, 9072−9081.
(76) Malmqvist, P.-A.; Roos, B. O. *Chem. Phys. Lett.* **1989**, *155*, 189−194.
(77) Engelbrecht, L.; Liu, B. *J. Chem. Phys.* **1983**, *78*, 3097−3106.
(78) McLean, A. D.; Lengsfield, B. H.; Pacansky, J.; Ellinger, Y. *J. Chem. Phys.* **1985**, *83*, 3567−3576.
(79) Lindh, R.; Barnes, L. A. *J. Chem. Phys.* **1994**, *100*, 224−237.
(80) Brueckner, K. A. *Phys. Rev.* **1954**, *96*, 508−516.
(81) Handy, N. C.; Pople, J. A.; Head-Gordon, M.; Raghavachari, K.; Trucks, G. W. *Chem. Phys. Lett.* **1989**, *164*, 185−192.
(82) Dykstra, C. E. *Chem. Phys. Lett.* **1977**, *45*, 466−469.
(83) Crawford, T. D.; Lee, T. J.; Handy, N. C.; Schaefer, H. F., III. *J. Chem. Phys.* **1997**, *107*, 9980−9984.
(84) Xie, Y.; Schaefer, H. F., III; Fu, X.-Y.; Liu, R.-Z. *J. Chem. Phys.* **1999**, *111*, 2532−2541.
(85) Stanton, J. F.; Gauss, J.; Bartlett, R. J. *J. Chem. Phys.* **1992**, *97*, 5554−5559.
(86) Gauss, J. In *The Encyclopedia of Computational Chemistry*; Schleyer, P. v. R., Allinger, N. L., Clark, T., Gasteiger, J., Kollman, P. A., Schaefer, H. F., III, Schreiner, P. R., Eds.; John Wiley & Sons: Chichester, U.K., 1998; Vol. 1, pp 615−636.
(87) Purvis, G. D.; Bartlett, R. J. *J. Chem. Phys.* **1982**, *76*, 1910−1918.
(88) Raghavachari, K.; Trucks, G. W.; Pople, J. A.; Head-Gordon, M. *Chem. Phys. Lett.* **1989**, *157*, 479−483.
(89) Bartlett, R. J.; Watts, J. D.; Kucharski, S. A.; Noga, J. *J. Chem. Phys. Lett.* **1989**, *165*, 513−522.
(90) Gill, P. M. W. In *The Encyclopedia of Computational Chemistry*; Schleyer, P. v. R., Allinger, N. L., Clark, T., Gasteiger, J., Kollman, P. A., Schaefer, H. F., III, Schreiner, P. R., Eds.; John Wiley & Sons: Chichester, U.K., 1998; Vol. 1, pp 678−689.
(91) Ayala, P. Y.; Schlegel, H. B. *J. Chem. Phys.* **1998**, *108*, 7560−7567.
(92) Kozlowski, P. M.; Rauhut, G.; Pulay, P. *J. Chem. Phys.* **1995**, *103*, 5650−5661.
(93) Archibong, E. F.; St-Amant, A. *Chem. Phys. Lett.* **1998**, *284*, 331−338.
(94) Duarte, H. A.; Proynov, E.; Salahub, D. R. *J. Chem. Phys.* **1998**, *109*, 26−35.
(95) Wang, S. G.; Schwarz, W. H. E. *J. Chem. Phys.* **1996**, *105*, 4641−4648.
(96) Beno, B. R.; Fennen, J.; Houk, K. N.; Lindner, H. J.; Hafner, K. *J. Am. Chem. Soc.* **1998**, *120*, 10490−10493.
(97) Haller, J.; Beno, B. R.; Houk, K. N. *J. Am. Chem. Soc.* **1998**, *120*, 6468−6472.
(98) Goldstein, E.; Beno, B. R.; Houk, K. N. *J. Am. Chem. Soc.* **1996**, *118*, 6036−6043.
(99) Goddard, J. D.; Chen, X.; Orlova, G. *J. Phys. Chem. A* **1999**, *103*, 4078−4084.
(100) Garavelli, M.; Bernardi, F.; Olivucci, M.; Robb, M. *J. Am. Chem. Soc.* **1998**, *120*, 10210−10222.
(101) Chen, W.-C.; Chuang, N.-y.; Yu, C.-h. *J. Phys. Chem. A* **1998**, *102*, 2584−2593.
(102) Gräfenstein, J.; Kraka, E.; Cremer, D. *Chem. Phys. Lett.* **1998**, *288*, 593−602.
(103) Gräfenstein, J.; Hjerpe, A. M.; Kraka, E.; Cremer, D. *J. Phys. Chem. A* **2000**, *104*, 1748−1761.
(104) Bettinger, H. F.; Schleyer, P. v. R.; Schreiner, P. R.; Schaefer, H. F., III. In *Modern Electronic Structure Theory and Applications to Organic Chemistry*; Davidson, E. L., Ed.; World Scientific: London, 1997; pp 89−171.
(105) Goddard, J. D.; Orlova, G. *J. Chem. Phys.* **1999**, *111*, 7705−7712.
(106) Cremer, D.; Kraka, E.; Szalay, P. G. *Chem. Phys. Lett.* **1998**, *292*, 97−109.
(107) Becke, A. D. *Phys. Rev. A* **1988**, *38*, 3098−3100.
(108) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785−789.
(109) Miehlich, B.; Savin, A.; Stoll, H.; Preuss, H. *Chem. Phys. Lett.* **1989**, *157*, 200−206.
(110) Hohenberg, P.; Kohn, W. *Phys. Rev. B* **1964**, *136*, 864−871.
(111) Kohn, W.; Sham, L. J. *Phys. Rev. A* **1965**, *140*, 1133−1138.
(112) Slater, J. C. In *Quantum Theory of Molecular and Solids*; McGraw-Hill: New York, 1974; Vol. 4.
(113) Perdew, J. P.; Wang, Y. *Phys. Rev. B* **1992**, *23*, 12947−12954.
(114) Perdew, J. P. *Phys. Rev. B* **1986**, *33*, 8822−8824.
(115) Perdew, J. P.; Zunger, A. *Phys. Rev. B* **1981**, *23*, 5048−5079.
(116) Vosko, S. H.; Wilk, L.; Nusair, M. *Can. J. Phys.* **1980**, *58*, 1200−1211.
(117) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648−5652.
(118) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; B. G. Johnson; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A. *Gaussian94*; Gaussian, Inc.: Pittsburgh, PA, 1995.
(119) Adamo, C.; Barone, V. *Chem. Phys. Lett.* **1997**, *274*, 242−250.
(120) Adamo, C.; Barone, V. *J. Comput. Chem.* **1998**, *19*, 418−429.
(121) Gill, P. M. W. *Mol. Phys.* **1996**, *89*, 433−445.
(122) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; G. E. Scuseria; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; J. A. Montgomery, J.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; J. M. Millam; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian98*; Gaussian, Inc.: Pittsburgh, PA, 1999.
(123) He, Y.; Gräfenstein, J.; Kraka, E.; Cremer, D. *Mol. Phys.* **2000**, *98*, 1639−1658.
(124) Dunning, T. H., Jr. *J. Chem. Phys.* **1989**, *90*, 1007−1023.
(125) Hariharan, P. C.; Pople, J. A. *Theor. Chimica Acta* **1973**, *28*, 213−222.
(126) Koseki, S.; Fujimura, Y.; Hirama, M. *J. Phys. Chem. A* **1999**, *103*, 7672−7675.
(127) Roth, W. R.; Hopf, H.; Wasser, T.; Zimmermann, H.; Werner, C. *Liebigs Ann.* **1996**, 1691−1695.
(128) Wenthold, P. G.; Lipton, M. A. *J. Am. Chem. Soc.* **2000**, *122*, 9265−9270.
(129) Schmittel, M.; Steffen, J. P.; Maywald, M.; Engels, B.; Helten, H.; Musch, P. *J. Chem. Soc., Perkin Trans. 2* **2001**, 1331−1339.